



RECEIVED
JUN 02 2003
TECH CENTER 1600/2900

Please amend the application as follows:

In the Specification:

Replace the present title, at the top of page 1, with the new title set forth below.

B1 FORMULATIONS COMPRISING AN INHIBITOR OF CARBOXYPEPTIDASE U AND A THROMBIN INHIBITOR

Replace the paragraph on page 1, lines 19-26 with the new paragraph below.

B2 Thrombin plays a central role in coagulation. It activates platelets, it converts fibrinogen into fibrin monomers, which polymerise spontaneously into filaments, and it activates factor XIII, which in turn crosslinks the polymer to insoluble fibrin. Thrombin further activates factor V and factor VIII in a positive feedback reaction. Inhibitors of thrombin are therefore expected to be effective anticoagulants by inhibition of platelets, fibrin formation and fibrin stabilization. By inhibiting the positive feedback mechanism they are expected to ~~exeert~~ exert inhibition early in the chain of events leading to coagulation and thrombosis.

Replace the paragraph on page 12, lines 17 to 29 with the new paragraph below.

B3 The term "heterocyclyl" denotes a substituted or unsubstituted, 4- to 10-membered monocyclic or multicyclic ring system in which one or more of the atoms in the ring or rings is an element other than carbon, for example nitrogen, oxygen or sulfur, especially 4-, 5- or 6-membered aromatic or ~~aliphatic~~ ~~heterocyclic~~ aliphatic heterocyclic groups, and includes, but is not limited to, azetidine, furan, thiophene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxthiolane, oxazolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, furazan, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, oxathiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, thiadiazine, dithiazine, azaindole, azaindoline, indole, indoline, naphthyridine groups, and shall be understood to include all isomers of the above identified groups. The term "azetidiny" shall for example ~~by~~ be understood to include the 2-, and 3-isomers and the terms "pyridyl" and "piperidiny" shall for example ~~by~~ be understood to include the 2-, 3-, and 4-isomers.

Replace the paragraph running from page 12, line 31 through page 13, line 3 with the new paragraph below.

B4 The term "cycloalkyl" denotes a saturated or unsaturated, substituted or unsubstituted, non-aromatic ring composed of 3, 4, 5, 6 or 7 carbon atoms, and includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ~~cycloheptyl~~ cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclopentadienyl, cyclohexadienyl and cycloheptadienyl groups.

Replace the paragraph on page 13, lines 7-9 with the new paragraph below.

B5 The term "aryl" denotes a substituted or unsubstituted C₆-C₁₄ aromatic hydrocarbon and includes, but is not limited to, phenyl, naphthyl, indenyl, ~~antracenyl~~, ~~fenantrenyl~~ anthracenyl, phenanthrenyl, and fluorenyl.

Replace the paragraph on page 13, lines 21 and 22 with the new paragraph below.

B6 The term "aroylamino" denotes an aroyl-N(Z)-group, wherein aroyl

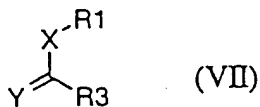
B6 conclude
and Z ~~is~~ are as defined above.

Replace the paragraph on page 13, lines 24 and 25 with the new paragraph below.

B7
The term "acylamino" denotes an acyl-N(Z)-group, wherein acyl and Z ~~is~~ are as defined above.

Replace step c) on page 16, lines 9-14 with the new step below.

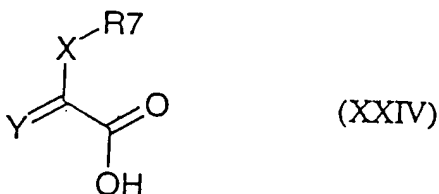
B8
(c) Compounds of the general Formula VI wherein R₁ and R₃ are as defined for Formula I and X is C(Z)₂ and R₂ is H can thereafter be converted to compounds of the general Formula VII,



by treatment with formaldehyde in the presence of a suitable base, such as Et₂NH, under standard conditions.

Replace step c) on page 22, lines 3-6 with the new step below.

B9 (c) Compounds of the general Formula XXIII can thereafter be converted to compounds of the general Formula XXIV,



by treatment with formaldehyde in the presence of a suitable base, such as Et₂NH, under standard conditions.

Replace the paragraph running from page 32, line 24 through page 33, line 3 with the new paragraph below.

B10 The term "condition in which inhibition of thrombin is required or desired" will be understood by those skilled in the art to include the following:

the treatment and/or prophylaxis of thrombosis and hypercoagulability in blood and tissues of animals including man. It is known that hypercoagulability may lead to thromboembolic diseases. Conditions associated with hypercoagulability and thromboembolic diseases which may be mentioned include inherited or acquired activated protein C

resistance, such as the factor V-mutation (factor V Leiden), and inherited or acquired deficiencies in antithrombin III, protein C, protein S, heparin cofactor II. Other conditions known to be associated with hypercoagulability and thromboembolic disease include circulating antiphospholipid antibodies (Lupus anticoagulant), ~~homocysteinemi~~ homocysteinemia, heparin-induced thrombocytopenia and defects in fibrinolysis.
